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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,633	03/17/2006	Douglas Spencer Millar	066828-0015	9313

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MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

EXAMINER

SAJJADI, FEREDOUN GHOTB

ART UNIT	PAPER NUMBER
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1633

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/536,633	Applicant(s) MILLAR ET AL.	
	Examiner Fereydoun G. Sajjadi	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/27/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response of February 23, 2007, to the Restriction Requirement dated January 25, 2006 has been entered. No claim were cancelled, amended, or newly added. Claims 22-41 are pending in the application.

37 CFR 1.121 (Problem with form of amendment)

The amendment filed on May 26, 2005 is objected to under 37 CFR 1.121(c). Claim 35, was not identified as a new claim, and is missing a status identifier and is therefore not in compliance with 37 CFR 1.121(c). While the amendment has been entered, please note that compliance with 37 CFR 1.121 is required for all future claim amendments. Failure to comply may result in non-entry of the amendment.

Election/Restrictions

Applicants' election of Group I (claims 22-41), drawn to a method of altering the methylation state of a cell comprising treating a first cell type with an extract, lysate, cellular component or mixture thereof derived from a second cell type, *in vitro* or *ex vivo*, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' election of species, stem cell as the first cell type, a normal cell as the second cell type, and bovine, with traverse, is further acknowledged. The traversal pertains to the election of species for a domestic animal, Applicants arguing that the members of the Markush Group are few in number and are closely related in that all are domestic animals. Applicants' arguments have been fully considered, but are not found persuasive. Each of the bovine, ovine, equine, poultry and porcine, comprise animals that are structurally and physiologically distinct compositions, that do not have a substantially common structure shared among them and are further capable of separate utility. As the distinct compositions are not encompassed by a single genus, they do not constitute a proper Markush group, and MPEP section 803.02 does not apply.

Art Unit: 1633

The different compositions require non-coextensive search and examination of their respective subject matter, thus imposing an undue burden on the examiner.

As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL.

Elected claims 22-41 are under current examination.

Information Disclosure Statement

The information disclosure statement filed 4/27/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been fully considered, since the WO 02/097065 document is not present in the instant application. Applicant is required to provide a copy of the missing references to be considered by the examiner.

Objections to the Specification/Abstract

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is unclear. Claim 22 is directed to a method wherein an extract, lysate cellular component or mixture thereof is derived from a cell. It is not clear how said derivation is

Art Unit: 1633

achieved. No active steps or descriptions for said derivation are provided in the claims.

Claim 35 is unclear. The claim recites various enzymes such as streptolysin O. The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 23-34 and 36-41 depend from claim 22 and do not include limitations that would obviate their rejections. Thus, they are included in the rejection.

Claim Rejections - 35 USC § 112 - Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-41 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for a method for altering a characteristic or state of a cell comprising treating stem cell with an agent capable of altering a characteristic or state in a cell, wherein the agent is an extract, lysate, cellular component or mixture thereof derived or obtained from a normal cell type having a desired characteristic or state; and determining the degree of alteration in the treated cell by measuring a methylation signature within the genome of the treated cell, wherein a given methylation signature is indicative of an altered characteristic or state of the treated cell, as claimed.

This rejection is based on several issues, each indicating an absence of an enabling disclosure for specifically altering the methylation signature of numerous genes within the genome of a stem cell, as outlined below. The deficiency was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by

Art Unit: 1633

Applicant would not have had to perform “undue experimentation” to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: “[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection.”

The instant specification does not provide an enabling disclosure for a method of altering the methylation signature of numerous genes within the genome of a stem cell to alter a characteristic or state of the stem cell, comprising treating said stem cell with an extract, lysate, cellular component or mixture thereof derived or obtained from a normal cell type having a desired characteristic state.

The specification does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because the description fails to provide what specific genomic sequences would require reprogramming of their methylation signatures to achieve a desired characteristic or desired state, or what constitutes a normal cell type, or what cellular components or mixtures thereof derived from a normal cell type may be used to treat a stem cell to achieve a desired characteristic.

The specification defines the term methylation signature within the genome of the cell as a group of cytosines within a region of the human genome that has a characteristic methylation signature which corresponds to a specific cell type (p. 4). The specification does not specifically define a normal cell, but states that the second cell type can be from an individual not suffering from a condition or state caused by an undesired characteristic of the first cell type (p. 5).

In the example provided, a cell extract from a Jurkat T cell line (second cell type) was used to treat 293 fibroblasts (first cell type; pp. 12-15). Figure 6 shows the methylation pattern of seven selected loci before and after reprogramming. It is assumed that the results depicted in Figure 6 correspond to treated fibroblast cells, as no stem cells were subjected to reprogramming or treatment (p. 28). The specification is silent on why the particular seven regions were chosen for analysis, or whether the methylation pattern of these genes corresponds only to T cells. The results showed that four of the genes tested were reprogrammed, one gene showed partial epigenetic programming and two genes were not successfully programmed, concluding: "thus the incorrect programming suggests that these cells may not be optimal for transplantation purposes" (p. 32). The specification is silent on the successful reprogramming of any cell for either the disclosed seven genes, or any of the other numerous genes in the genome.

Regarding the claimed treatment of the stem cells with any cellular component or mixtures derived from a normal cell, the specification is silent on the reprogramming abilities of any cellular components, that would include membrane or extracellular matrix proteins. The prior art is further silent on the ability of any of the numerous extracellular components or membrane proteins to induce reprogramming of a stem cell, or any other cell type.

The specification further states: "Since, in general, increased methylation leads to shutting down of gene activity, whereas demethylation leads to an increase in gene activity, we have sought to find those genes whose activity status alters during the aging process...we have used adult CD34+ stem cells from mobilized peripheral blood from individuals of different ages" (pp. 27-28, bridging). However, the prior art of Sakashita et al. teaches that the p15 gene in CD34+ cord blood or bone marrow stem cells in exon 1 and promoter region is either fully methylated or completely unmethylated, and that treatment of the CD34+ stem cells with GM-CSF resulted in an increase in allelic methylation in the two p15 gene regions to approximately 50-60% until day 7 after cytokine stimulation, then decreased to less than 10% after 21 days (Abstract). The authors concluding that a dynamic DNA methylation change is involved in the expression of the tissue specific gene during myeloid development (first column, p. 1204). Thus, the methylation state of a stem cell is variable and undergoes dynamic change. Hence it would not be predictable to necessarily correlate such changes with a desired characteristic of state. Moreover, with over 30,000 expressed genes, it would require undue further

Art Unit: 1633

experimentation on the part of a person of ordinary skill in the art to determine the methylation signature of these genes and to further correlated the methylation states with “normality” or a desired state for the over 300 cell types in a human being.

The post-filing review of transdifferentiation or reprogramming, Hakelien et al. (Cloning & Stem Cells 4:379-387; 2002) states that *in vitro* reprogramming assays involve extensive cell manipulation and thus, the application of this technology to produce replacement cells for therapeutic purposes requires significant developments and a large body of data is needed before this system can be applied to the generation of cells used for therapy in human patients. (first column, p. 386).

As the instant specification is devoid of any actual data regarding the reprogramming of the methylation pattern for any region of the genome of a stem cell (or any other cell type), by treatment with any cellular component of any normal cell type, the instantly claimed method is simply an invitation to a person of skill in the art to engage in further undue experimentation, to test and determine the validity of the claimed method. Please note “case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves.” *In re Gardner* 166 USPQ 138 (CCPA) 1970.

As the prior art is silent on which genes or genomic regions would require alteration of their methylation signatures to achieve a desired characteristic or desired state for a stem cell, the person of skill in the art would have to perform a large amount of experimentation to identify such sequences following a genome wide sequence analysis and correlation study. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation which sequence(s) or genomic regions would require alteration of their methylation signatures or how such alterations may be brought about via any cellular component. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-31, 37-38, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakashita et al. (J. Clin. Invest. 108:1195-1204; 2001).

When given their broadest reasonable interpretation, the claims encompass a method comprising treating a stem cell with a cellular component obtained from a normal cell type and measuring a methylation signature within the genome of the treated cell.

Sakashita et al. teach the treatment of cord blood and bone marrow CD34+ stem cells with either GM-CSF or in combination with stem cell factor, followed by bisulfite genomic sequencing, and determination of the methylation of a number of CpG dinucleotide sites in the promoter and exon 1 of the p15 gene following said treatment (Abstract).

Therefore by teaching all the limitations of claims 22-31, 37-38, 40 and 41, Sakashita et al. anticipate the instant invention as claimed.

Conclusion

Claims 22-41 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1633

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, AU 1633

